Oxybutynin Chloride Extended-Release Tablets

DEFINITION

Oxybutynin Chloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$).

IDENTIFICATION

• **A. Infrared Absorption** ⟨197⟩

Standard: Dissolve 15 mg of USP Oxybutynin Chloride RS in 5 mL of water. Adjust with 0.1 N sodium hydroxide to a pH of between 7 and 8. Extract the solution twice with 10 mL of ether. Combine the extracts, evaporate the ether, and dry under vacuum over silica gel for at least 30 min. Redissolve the dried residue in a small amount of acetone, transfer the solution to an IR salt plate, and evaporate to cast a thin film.

Sample: Add a quantity of finely powdered Tablets, equivalent to about 15 mg of oxybutynin chloride, to 5 mL of water per Tablet. Mix for 1 min. Adjust with 0.1 N sodium hydroxide to a pH between 7 and 8. Extract the solution twice with 10 mL of ether. Combine the extracts, evaporate the ether, and dry under vacuum over silica gel for at least 30 min. Redissolve the dried residue in a small amount of acetone, transfer the solution to an IR salt plate, and evaporate to cast a thin film.

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Diluent: Use water adjusted with phosphoric acid to a pH of 3.5.

Solution A: Methanol and acetonitrile (1:1)

Mobile phase: Acetonitrile, triethylamine, and water (700:3:1300). Adjust with phosphoric acid to a pH of 3.9.

Impurity stock solution: 0.11 mg/mL of USP Oxybutynin Related Compound A RS in acetonitrile

Standard stock solution: 0.37 mg/mL of USP Oxybutynin Chloride RS in acetonitrile

Standard solution: 0.1 mg/mL in *Diluent*, from the *Standard stock solution*

Sample solution

For Tablets that contain 5 mg of oxybutynin chloride: Place 10 Tablets in a 500-mL volumetric flask, add 150 mL of *Solution A*, and stir for at least 4 h or until dissolved. Dilute with *Diluent* to volume. Mix thoroughly, centrifuge, and use the clear supernatant.

For Tablets that contain 10 mg or more of oxybutynin chloride: Place 10 Tablets in a 1000-mL volumetric flask, add 300 mL of *Solution A*, and stir for at least 4 h or until dissolved. Dilute with *Diluent* to volume. If necessary, make a further dilution with *Diluent* to obtain a solution having a final concentration equivalent to 0.1 mg/mL of oxybutynin chloride. Mix thoroughly, centrifuge, and use the clear supernatant.

System suitability solution: Transfer 10 mL of *Standard stock solution* and 1 mL of the *Impurity stock solution* to a 100-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; packing L11

Flow rate: 1.5 mL/min

Injection size: 50 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for oxybutynin and oxybutynin related compound A are about 1.0 and 1.6, respectively.]

Suitability requirements

Resolution: NLT 1.5 between oxybutynin and oxybutynin related compound A

Tailing factor: Greater than 0.75 and NMT 2.5 for each peak

Relative standard deviation: NMT 3% for each compound for six replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Oxybutynin Chloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of oxybutynin chloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Medium: Simulated gastric fluid without enzyme; 50 mL

Apparatus 7: See *Drug Release* ⟨724⟩, 30 cycles/min; 2- to 3-cm amplitude, at 37.0 ± 0.5°

Times: 4, 10, and 24 h

Solution A: 4.83 g/L of monobasic sodium phosphate in water. Add 2.3 mL/L of triethylamine, and adjust with phosphoric acid to a pH of 2.2 ± 0.2.

Mobile phase: Acetonitrile and *Solution A* (7:13)

Solution B: To 1 L of water add phosphoric acid dropwise to a pH of 3.5, and mix well.

Standard stock solutions: 250, 300, and 350 µg/mL each of USP Oxybutynin RS in acetonitrile

Standard solutions: Prepare a series of dilutions of the *Standard stock solutions* in *Solution B* having final concentrations similar to those expected in the *Sample solution*.

Sample solution: Use portions of the solution under test. If the solution is cloudy, centrifuge at 2000 rpm for 10 min, and use the supernatant.

System suitability solution: Use a medium range *Standard solution* of USP Oxybutynin Chloride RS.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

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Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 5-cm; packing L11
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection size: 50 µL

System suitability
Sample: *System suitability solution*
Suitability requirements
Tailing factor: Greater than 0.5 and less than 2.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solutions* and *Sample solution*
Construct a calibration curve by plotting the peak response versus concentration of the *Standard solutions*. A weighing factor, $1/x$, is applied to the regression line of the calibration curve to enhance the accuracy of the low standard concentrations. Determine the percentage of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved in each interval from a linear regression analysis of the calibration curve.

Tolerances: See *Tables 1* and *2*.

Table 1. For Tablets labeled to contain 5 or 10 mg of oxybutynin chloride

Time (h)	Amount Dissolved
4	NMT 20%
10	34.5%–59.5%
24	NLT 80%

Table 2. For Tablets labeled to contain 15 mg of oxybutynin chloride

Time (h)	Amount Dissolved
4	NMT 20%
10	34.5%–59.5%
24	NLT 75%

The percentages of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.
Acid stage medium: Simulated gastric fluid, without enzymes, pH 1.2 ± 0.05; 250 mL (first row)
Buffer stage medium: Simulated intestinal fluid, without enzymes, pH 6.8 ± 0.1; 250 mL (rows 2–4)
Apparatus 3: 25 dips/min; 20-mesh polypropylene screen on top and bottom; 30 s drip time
Times: 2 h in the •*Acid stage medium*• (RB 1-May-2011) (first row); 4, 8, and 16 h •(corresponding to 2, 6, and 14 h after changing the medium)• (RB 1-May-2011) in the •*Buffer stage medium*• (RB 1-May-2011) (rows 2–4)
Solution A: Transfer 1 mL of triethylamine to 1000 mL of water. Adjust with phosphoric acid to a pH of 3.50 ± 0.05.
Mobile phase: Acetonitrile and *Solution A* (4:1)
Standard stock solution: 0.2 mg/mL of USP Oxybutynin Chloride RS in *Acid stage medium*
Working standard solution: Transfer 5.0 mL of the *Standard stock solution* for Tablets labeled to contain 5 mg, or transfer 10 mL for Tablets labeled to contain 10 mg, to a 100-mL volumetric flask. Dilute with *Buffer stage medium* to volume.

Sample solution: Centrifuge a portion of the solution under test at approximately 3000 rpm for 10 min. Use the supernatant.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 203 nm
Column: 4.6-mm × 25-cm; packing L7
Flow rate: 1.5 mL/min
Injection size: 25 µL

System suitability
Sample: *Working standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 3.0%

Analysis
Samples: *Working standard solution* and *Sample solution*
Calculate the percentage of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved at each time point (C_{T2}, C_{T4}, C_{T8}, C_{T16}):

$$\bullet C_i = (r_U/r_S) \times (C_S/L) \times V \times 100 \bullet \text{ (RB 1-May-2011)}$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Working standard solution*
C_S = concentration of the *Working standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 250 mL
C_{T2} = percentage dissolved at 2 h, C_2
C_{T4} = percentage dissolved at 4 h, $C_2 + C_4$
C_{T8} = percentage dissolved at 8 h, $C_2 + C_4 + C_8$
C_{T16} = percentage dissolved at 16 h, $C_2 + C_4 + C_8 + C_{16}$

Tolerances: See *Tables 3* and *4*.

•Table 3. For Tablets labeled to contain 5 mg or 10 mg• (RB 1-Aug-2010)

Time (h)	Amount Dissolved
2	0%–10%
4	10%–30%
8	40%–65%
16	NLT 80%

•Table 4. For Tablets labeled to contain 15 mg

Time (h)	Amount Dissolved
2	0%–10%
4	10%–30%
8	35%–65%
16	NLT 75%

The percentages of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
Medium: Simulated gastric fluid without enzyme; 50 mL
Apparatus 7: See *Drug Release* ⟨724⟩. Use acrylic rods. 30 dips/min, 37.0 ± 0.5°, 10 s drip time. Dip time interval: row 1, 1 h; row 2, 3 h; row 3, 6 h; row 4, 5 h; row 5, 9 h.
Times: 4, 10, and 24 h
pH 2.3 phosphate buffer: 3.4 mg/mL of monobasic potassium phosphate in water. Adjust with phosphoric acid or 2 N potassium hydroxide to a pH of 2.30 ± 0.05.

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Standard solution: *L*/200 (mg/mL) of USP Oxybutynin Chloride RS in *Medium*, where *L* is the Tablet label claim, in mg
Sample solution: Pass a portion of the solution under test through a suitable nylon filter of 0.45-µm pore size, discarding the first few mL.
Mobile phase: *pH 2.3 phosphate buffer* and acetonitrile (7:3)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; packing L10
Flow rate: 1.0 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis: Calculate the amount, in mg, of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved at each time interval:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 50 mL

Calculate the percentage of oxybutynin dissolved:

Result = Σ(amount dissolved at current time interval + amount dissolved at previous time intervals) × 100/*L*

Tolerances: See *Table 5*.

Table 5

Time (h)	Amount Dissolved
4	NMT 25%
10	40%–65%
24	NLT 75%

The percentages of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 4: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.
Acid stage medium: 0.1 N hydrochloric acid; 900 mL
Buffer stage medium: pH 6.0 sodium phosphate buffer with 0.2% of sodium lauryl sulfate; 900 mL
Apparatus 2: 50 rpm, with sinkers. [NOTE—A suitable sinker is available as catalog number CAPWHT-2S from www.QLA-LLC.com]
Times: 2 h in the *Acid stage medium*; 4, 6, and 14 h (corresponding to 2, 4, 12 h after changing the medium) in the *Buffer stage medium*
Standard solution: *L*/1000 (mg/mL) of USP Oxybutynin Chloride RS in *Buffer stage medium*, where *L* is the Tablet label claim, in mg
Sample solution: Pass a portion of the solution under test through a suitable PVDF filter of 0.45-µm pore size.
pH 3.5 phosphate buffer: 6.94 mg/mL of monobasic potassium phosphate in water. Adjust with diluted phosphoric acid to a pH of 3.50 ± 0.05.
Mobile phase: *pH 3.5 phosphate buffer* and acetonitrile (1:1)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; packing L7
Flow rate: 1.0 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis: Calculate the concentration (mg/mL) of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) ($C_i$) at each time point:

$$C_i = (r_U/r_S) \times C_S$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

Calculate the cumulative percentage of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved ($Q_i$) at each time point ($i$):
At $i = 1$

$$Q_1 = (C_1 \times V/L) \times 100$$

At i = 2 to n

$$\frac{(C_1 \times 900) + \sum_{j=2}^{n-1} C_j V_s + C_n \times [900 - (n-2)V_s] \times 100}{L}$$

i = 1, 2, ..., n
j = 2, 3, ..., n–1
V_S = sampling volume (mL)
C_i = concentration of oxybutynin chloride in the *Sample solution* at time point i (mg/mL)
C_j = concentration of oxybutynin chloride in the *Sample solution* at time point 2 through n–1 (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 6*.

Table 6

Time (h)	Amount Dissolved
2	NMT 10%
4	10%–40%
6	40%–75%
14	NLT 85%

The percentages of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩. ●(RB 1-Aug-2010)

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩: Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**
Diluent, Solution A, Mobile phase, Impurity stock solution, System suitability solution, Chromatographic system, Sample solution, and **System suitability:** Proceed as directed in the *Assay*.
Impurity standard solution: 1 µg/mL of USP Oxybutynin Related Compound A RS in *Diluent*, from the *Impurity stock solution*

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Analysis

Samples: *Impurity standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response for each impurity from the *Sample solution*
r_S = peak response from the *Impurity standard solution*
C_S = concentration of USP Oxybutynin Related Compound A RS in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

[NOTE—Disregard any peak less than 0.1%.]

Acceptance criteria

Individual impurities: NMT 1% of oxybutynin related compound A is found.

Total impurities: NMT 2%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Oxybutynin Chloride RS
  USP Oxybutynin Related Compound A RS
  Phenylcyclohexylglycolic acid.
  $C_{14}H_{18}O_3$ 234.30

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